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Signature	
Date	May 30, 2003

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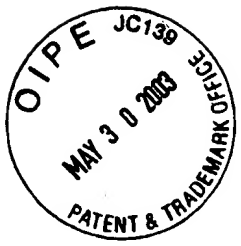

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Purnendu K. Dasgupta	
Application No. 09/780,434 ✓	Group Art Unit 1743
Filed: February 12, 2001	Examiner: Soderquist
For: CONTINUOUS ON-LINE TITRATION BY FEEDBACK BASED RATIOMETRY	

RESPONSE TO OFFICE ACTION

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313

Sir:

Responsive to the Office Action dated March 27, 2003, applicants respectively request reconsideration of the claims now in the application in view of the following comments.

Claims 1-15 remain in the application. Claim 1 is directed to a method of titration which includes the steps of supplying a sample and a titrant to a confluence point, controlling the rate of flow of titrant by varying a pump to increase or decrease its rate of flow, detecting a change in the mixed titrant and sample stream, and changing the rate of flow of the titrant from increasing to

decreasing, or vice versa, upon detection of a change in the mixed stream. Dependent Claims 2-15 add various steps to the method, or provide details of the recited steps. For example, Claim 2 defines the step of supplying a control voltage of a specified waveform, Claim 3 defines the process of changing the rate of flow, and Claim 4 defines detecting changes during an increasing and a decreasing slope to compensate for the lag time, and determining titration equivalence flow.

Claim 6 is an independent claim directed to a feedback controlled titration system in which the detection of a change in a monitored property during changes in titrant flow in a first direction results in a change in the direction of change of the titrant flow, while Claims 7-10 are dependent on this claim, and define the waveforms of the ratios of change.

Claim 11 is directed to a feedback controlled titration method wherein the titrant flow rate pattern is varied upon detection of a change in a monitored property, and Claims 12-15 are dependent on that claim. The dependent claims define the manner in which the flow rate pattern is changed.

The key to the present invention is the detection of a set point, which may or may not correspond to the equivalence point, to cause the ramp rate of a variable flow rate pump (or the ramp rate of a reagent generator) to be immediately reversed. The prior art relied on in the Office Action utterly fails to disclose this feedback operation, as is admitted in the Office Action, and

accordingly the claims are believed to be clearly patentable.

In the Office Action, Claims 1-15 were rejected under 35 USC 103(b) as being unpatentable over Nagy in view of Garcia and Becket, it being asserted that it "would have been obvious . . . to use the feedback of Nagy to control the flow of the titrant in the manner taught by Nagy". The basis for this rejection is the asserted teaching of Becket that "feedback allows control of the titrant in the region of the endpoint or the equivalence point of the titration.

Applicants are not quite sure how to respond to this rejection, since the Office Action does not specify how the claims are affected by the asserted teachings of the cited references. This is particularly the case since page 4 of the Office Action states, in lines 3 and 4, that "Nagy does not teach how the feedback is used", yet at page 5, line 9 of the Office Action it is said that it would be obvious to "use the feedback of Nagy to control the flow of titrant in the manner taught by Nagy".

Nagy does not teach, or even suggest, the process of the present invention, as set out in the claims. Instead, Nagy operates in a fixed program in which a reagent flow goes from zero to some present maximum and then reverses itself, regardless of whether the sample was titrated within the first 10 seconds of a 5 minute ramp, and this simply wastes time and valuable reagent.

Although Nagy mentions "feedback" in column 5, there is not a single example in the Nagy patent concerning the use of feedback, much less using

feedback in a manner that uses it to reverse the ramp rate. Not only is there no such teaching in Nagy, but there is no such teaching in any of the other references cited either by applicants or in the Office Action. If a finite concentration of the analyte is present in the sample, in the method of the present invention, the variable titrant pump rate never goes to zero and rarely will go to the maximum value allowable by the algorithm because that would result in the final mixture containing no reagent at all.

Becket describes a system in which a base solution is titrated with an acid titrant in a flow system, the pH is monitored with a pH electrode and this is used in a feedback loop control to change the titrant pump rate to maintain the system precisely at the equivalence point. Blaedel and Laessig in 1964 and 1965 described exactly this technique, and it is discussed in the application with respect to Figs. 1 and 4. Using the best principle of feedback-based control that is presently practiced in the chemical process industry (proportional integral derivative (PID) control), such a controller is able to maintain a pump rate at the exact point where the mixed solution is maintained at the desired point of neutralization (as monitored by the status of an optical indicator) as indicated by a flat line in the plot (in Figure 4, this occurs for cases 1a (second time only), 2a (both times), 2b (first time only), 2c (second time only)). Most of the other times, the controller is unable to maintain the system at the neutralization point, and the system keeps on

oscillating. Indeed, the system is not reproducible, and under identical conditions (e.g., for cases 2b and 2c) sometimes the system is stable, sometimes it goes into oscillation. Those who are versed in the art of titration, know that regardless of how the titration is followed, e.g., by potentiometric or optical means, the desired characteristic in a titration is that the signal changes most abruptly around the equivalence point. To try to maintain a system precisely at the point where it is most susceptible to any change in the flow of the titrant is a nightmare for any control system. For optically monitored titrations (which are practically bistable (one color or the other), it is the equivalent of trying to keep a see-saw perfectly balanced. Indeed, the fact it was possible to maintain the system under stable feedback in a few cases in Figure 4 was due to the fact that the sample concentration was invariant in that experiment. In a real process situation, the analyte concentration will vary with time, and maintaining the system at equivalence by feedback will be essentially impossible - equivalent to maintaining a see-saw at balance while one person juggles bowling balls in an unpredictable manner by moving the other person backward and forward as the control mechanism.

It may be made to work in a method where around the defined setpoint the monitored property changes only slowly with the rate of the titration, but as a general rule it cannot and does not work. For a strong acid - strong base type of titration, the most common type of titration, the pH for example,

changes most rapidly/steeply near the equivalence point. This is why in the 40 years since Blaedel and Laessig, no one has used such a technique in practice as a general method.

Figures 5 and 6 in the present application show how the system works essentially according to Nagy. Actually the illustration is somewhat more efficient than the Nagy system because it does not actually go down to zero reagent flow (reagent flow is linearly related to the control voltage V_c plotted as the abscissa).

Referring to Figure 5, note that in response to the triangular wave V_c controlling the titrant flow the detector output D_{out} (an optical detector is used in these experiments) basically executes a rectangular wave pattern. The yellow form of the indicator has practically no absorption at the monitoring wavelength. Thus at the high end, D_{out} is flat. At the low end, even after the indicator turns blue, further increase of F_B brings still more indicator in the system (since the indicator is incorporated in the titrant) and at the low end, D_{out} is not completely flat but executes a shallow V.

A plot of the D_{out} as a function of V_c is shown in Fig. 6 for 10 titrations each of (a) 50 mM and (b) 100 mM HCl. It is possible to visualize the conventional titration plot in Figure 6 by focusing on the ascending or descending halves individually. V_E essentially represents the abscissa value corresponding to the center of mass of the parallelogram (about V_c = 2.5 and

3.5 V, respectively, for Figures 6a and 6b). There is no question that the Nagy method works as claimed in the '657 patent. However, Figure 6 also shows very clearly that the scheme results in large amounts of time being spent in a useless manner. For example, in Figure 6a, the system unnecessarily scans in the V_c = 1-2 and 3-5 V range and similarly it spends unnecessary time in the titration of Figure 6b in the V_c = 1-3 and 4-5 V range. Indeed, had we gone down to 0 V, as Nagy recommends, the titration would have wasted even more time. The useful information is present in only a 1V window and in a 0-5 volt scan using Nagy's system; 80% of the time and titrant will be spent in a useless manner.

Titrations carried out according to the present invention that are correspondent to Figures 5 and 6 carried out by Nagy's method are respectively shown in Figures 7 and 9. Note Figure 7 shows how ramp reversal occurs each time the detector set point is crossed. Note in Figure 9 how the same identical titrations as in Figure 6 are carried out in Figure 9 by scanning the control voltage (i.e., the titrant flow rate) over a much smaller range, thus minimizing time and waste. The resulting economy is reflected in the results; with the present invention titrations requiring as little as 3 s consume as little as 0.012 mL of titrant. Nagy uses a ramp time of 30 s to 5 minute and clearly says that " . . . reducing the length of the cycles is limited by the fact that the reagent flow program may be distorted . . ." (Col 6, lines 24-26). Although a titration

rate up to 200 per hour is claimed (Col 6 line 37) this is in fact impossible if the minimum ramp time is 30 s (Col 2 line 66). Nagy uses a flow rate of 5-10 mL/min (Col 7 line 68), a titration minimally requiring 30 s will consume 2.5 to 5.0 mL titrant, i.e., it requires 10 times longer and consumes 200-400 times more titrant than the method of the present invention, as claimed herein.

It is true that the Nagy patent mentions "feedback" in its descriptions (Col 5 line 12), but what the feedback connotes or what is being accomplished with the "feedback" is not discussed with any clarity, nor are any examples given in this patent or any of the many triangular wave titration papers that have since been published that would indicate that the term "feedback" means immediate ramp reversal upon crossing a setpoint. To the contrary, everything in the '657 patent indicates that feedback-based ramp reversal was not contemplated, and that no such teaching was contemplated is further confirmed by lack of anyone practicing such feedback, who nevertheless cited Nagy .

Nagy makes clear that in its method, reagent flow rate decreases to zero (Col 8 line 29), and elsewhere also make it clear how going to zero titrant flow is an important and critical part of the disclosed procedure (Col 5 paragraph beginning line 47, Col 6 line 12-13).

A careful reading of the '657 patent makes it clear that the inventors contemplated ramping up the reagent flow rate from zero to some maximum

and then ramping it back down to zero. There is no indication anywhere that the practice involves anything other than operating between these fixed minimum (zero) and maximum (nonzero) limits each and every time, no matter what the sample concentration. The minimum and maximum reagent addition rates, in turn, must at least correspond to the minimum and maximum analyte concentrations that need to be titrated. In other words, the scan limits are predetermined.

If "feedback" is used in Nagy, the reading of the relevant section of Col 5 of Nagy indicates that it at best means that this may be used to alter reagent addition rate, for regardless of the sample concentration, as that concentration changes, the low and high limits of the reagent addition rates are not changed. In marked and direct contrast, Figure 8 of the present application shows how V_c (this corresponds to the reagent addition rate) limits are not fixed (this is the dense trace in the upper panel of Figure 8) but change as the analyte concentration changes continuously.

In summary, the Nagy patent alone or in combination with any other cited reference does not make the present invention (which is far more time and reagent-efficient) obvious. A careful and thorough reading of the Nagy patent, the Becket patent and the Garcia paper can only confirm this conclusion.

In view of the foregoing, favorable reconsideration of the application and

allowance of the claims is solicited.

Respectfully submitted,
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